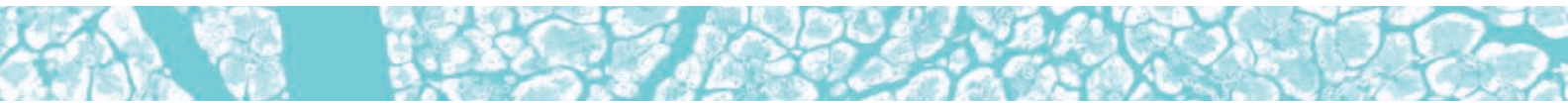


BIOLOGY OF AGING

Research Today
for a Healthier
Tomorrow



BIOLOGY OF AGING

Research Today for a Healthier Tomorrow

AGING UNDER THE MICROSCOPE

- 4 **What is aging?**
- 6 **Living long and well: Can we do both? Are they the same?**
- 9 **Is what's good for mice good for men?**

GENETICS

- 13 **Is aging in our genes?**
- 14 **How can we find aging genes in humans?**
- 18 **What happens when DNA becomes damaged?**

METABOLISM

- 23 **Does stress really shorten your life?**
- 27 **Does how much you eat affect how long you live?**

IMMUNE SYSTEM

- 31 **Can your immune system still defend you as you age?**

THE PROMISE OF RESEARCH

- 35 **Past, present, and future**

36 GLOSSARY

37 BIBLIOGRAPHY

The National Institute on Aging (NIA), part of the National Institutes of Health at the U.S. Department of Health and Human Services, was established to help improve the health and well-being of older people through research. NIA conducts and supports research on the medical, social, and behavioral aspects of aging. This mission is carried out through NIA's Intramural Research Program composed of staff scientists in Baltimore and Bethesda, Maryland, and through its Extramural Research Program, which funds researchers at major institutions across the United States and internationally. *Biology of Aging: Research Today for a Healthier Tomorrow* describes some of NIA's exciting findings about the basic biology of aging and points to directions for future investigation.

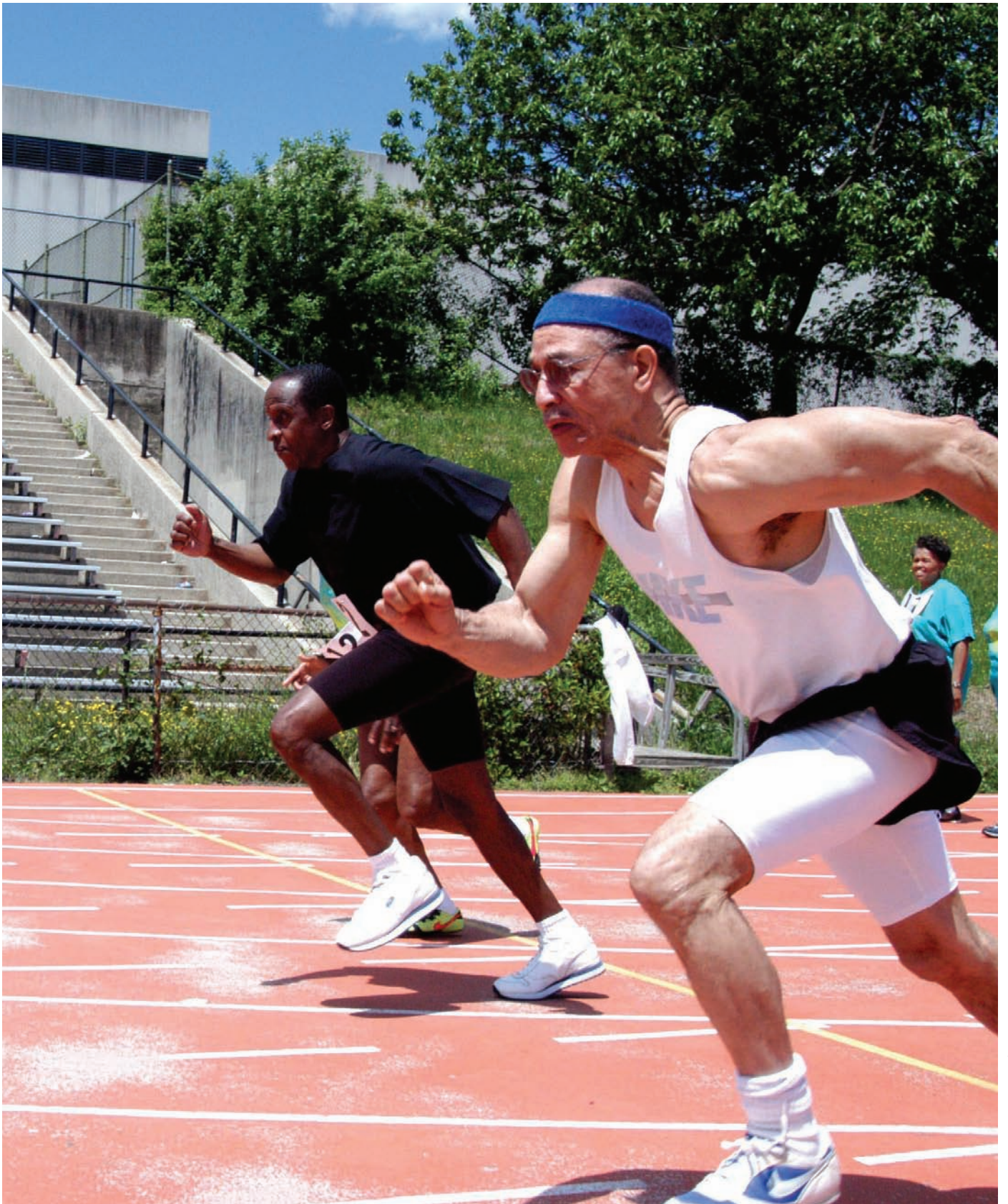


PHOTO CREDIT: MARTY KATZ, WWW.MARTYKATZ.COM

AGING UNDER THE MICROSCOPE

We marvel at the 90-year-old who still gets up every day and goes to work. And, it is a genuine thrill to celebrate a relative's 100th birthday. Yet our feelings about aging are complex.

We may want to live forever, but who looks forward to getting old? We hope we're vigorous right up until the very end. Still, day-to-day, many of us make unhealthy choices that could put our future at risk.

From the beginning of time, people have tried to understand aging. Almost every culture has a mythology to explain it. As we grow up, tales of eternal youth pique our curiosity. And, it is these musings that may provide just the spark needed to ignite a budding scientist. There's the little girl, excited to visit her grandmother, who asks her parents how someone so spunky and fun could be so old. Or, the 3rd grader who, after watching in awe as a caterpillar spins a cocoon and then days later emerges as a butterfly, peppers the teacher with questions

about this magical transformation. These are the types of questions and kinds of experiences that could stimulate a lifelong quest to explore what happens as we age.

Since the National Institute on Aging (NIA) was established at the National Institutes of Health (NIH) in 1974, scientists asking just such questions have learned a great deal about the processes associated with the biology of aging. For scientists who study aging—called gerontologists—this is an exciting time. Technology today supports research that years ago would have seemed possible only in a science fiction novel. And, a scientific community that values active collaboration as well as individual scientific achievement has helped to move research forward faster than ever before.

Over centuries, theories about aging have emerged and faded, but the true nature of the aging process is still uncertain. The fact is—aging is a part of everyone’s life. But the facts of aging—what is happening on a biochemical, genetic, and physiological level—remain rich for exploration.

This booklet introduces some key areas of research into the biology of aging. Each area is a part of a larger field of scientific inquiry. You can look at each topic individually, or you can step back to see how they fit together in a lattice-work, interwoven to help us better understand aging processes. Research on aging is dynamic, constantly evolving based on new discoveries, and so this booklet also keeps an open eye on the future, as today’s research provides the strongest hints of things to come.

What is aging?

In the broadest sense, aging reflects all the changes that occur over the course of life. You grow. You develop. You reach maturity. To the young, aging is exciting—it leads to later bedtimes and curfews, and more independence. By middle age, another candle seems to fill up the top of the birthday cake. It’s hard not to notice some harmless cosmetic changes like gray hair and wrinkles. Middle age also is the time when people begin to notice a fair amount of physical decline. Even the most athletically fit cannot escape these changes. Take marathon runners, for example. An NIA-funded study found that their record times increased with age—aging

literally slowed down the runners. Although some physical decline may be a normal result of aging, the reasons for these changes are of particular interest to gerontologists.

Gerontologists look for what distinguishes normal aging from disease, as well as explore why older adults are increasingly vulnerable to disease and disability. They also try to understand why these health threats take a higher toll on older bodies. Since 1958, NIA’s Baltimore Longitudinal Study of Aging (BLSA) has been observing and reporting on these kinds of questions. As with any longitudinal study, the BLSA repeatedly evaluates people over time rather than comparing a group of young people to a group of old people, as in a cross-sectional study. Using this approach, BLSA scientists have observed, for example, that people who have no evidence of ear problems or noise-induced hearing loss still lose some of their hearing with age—that’s normal. Using brain scans to learn if cognitive changes can be related to structural changes in the brain, BLSA scientists discovered that even people who remain healthy and maintain good brain function late in life lose a significant amount of brain volume during normal aging.

However, some changes that we have long thought of as normal aging can be, in fact, the signs of a potential disease. Take, for example, sudden changes in personality. A common belief is that people become cranky, depressed, and withdrawn as they get older. But an analysis of long-term data from the BLSA showed that an adult’s personality

POSSIBLE PATHWAYS LEADING TO AGING

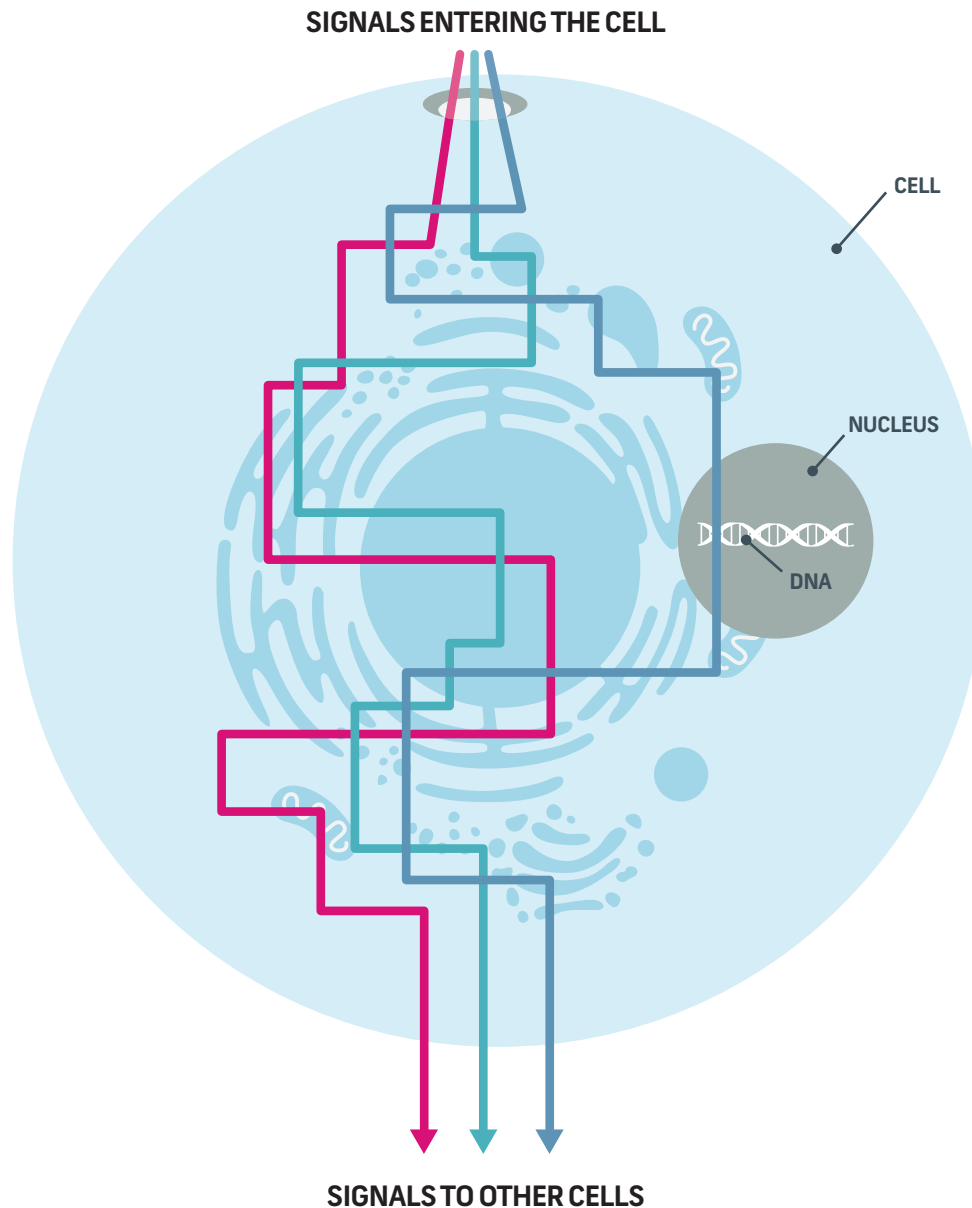


ILLUSTRATION AND INFORMATION ADAPTED FROM WWW.GENOME.GOV

To answer questions about why and how we age, some scientists look for mechanisms or pathways in the body that lead to aging. Our cells constantly receive cues from both inside and outside the body, prompted by such things as injury, infection, stress, or even food. To react and adjust to these cues, cells send and receive signals through biological pathways. Some of the most common are involved in metabolism, the regulation of genes, and the transmission of signals. These pathways may also be important to aging.

generally does not change much after age 30. People who are cheerful and assertive when they are younger will likely be the same when they are age 80. The BLSA finding suggests that significant changes in personality are not due to normal aging, but instead may be early signs of disease or dementia.

The rate and progression of cellular aging can vary greatly from person to person. But generally, over time, aging affects the cells of every major organ of the body. Changes can start early. Some impact our health and function more seriously than others. For instance, around the age of 20, lung tissue starts to lose elasticity, and the muscles of the rib cage slowly begin to shrink. As a result, the maximum amount of air you can inhale decreases. In the gut, production of digestive enzymes diminishes, affecting your ability to absorb foods properly and maintain a nutritional balance. Blood vessels in your heart accumulate fatty deposits and lose flexibility to varying degrees, resulting in what used to be called “hardening of the arteries” or atherosclerosis. Over time, women’s vaginal fluid production decreases, and sexual tissues atrophy. In men, aging decreases sperm production, and the prostate can become enlarged.

Scientists are increasingly successful at detailing these age-related differences because of studies like the BLSA. Yet studies that observe aging do not identify the reasons for age-related changes, and, therefore, can only go so far toward explaining aging. Questions remain at the most basic level about what triggers aging in our tissues and cells, why it

occurs, and what are the biological processes underlying these changes. Scientists look deep into our cells and the cells of laboratory animals to find answers. What they learn today about aging at the cellular and molecular levels may, ultimately, lead to new and better ways to live a longer, healthier life.

Living long and well: Can we do both? Are they the same?

You can hardly turn on your computer these days without being bombarded with advertisements that pop up trying to convince you of the power of a pill that will make you live longer or a cream that will help to revive your youthful vigor and appearance. The search for



ways to stop or reverse the aging process is a near-obsession in popular culture. The likelihood of discovering a scientifically proven “anti-aging” elixir is slim, but researchers believe their work will reveal ways to improve a person’s ability to live a longer, healthier life. They express these goals in terms of “lifespan” and “health span,” respectively.

Lifespan is the length of life for an organism. For instance, if you live to age 99, that would be your lifespan. Maximal lifespan is the maximum number of years of life observed in a specific population. It differs from species to species. The maximum recorded lifespan for humans, reported in 2010, was 122.5 years for females and 116 years for males.

Lifespan is a common measurement in aging research. That’s because it is clear-cut and easy to measure—an organism is either alive or dead. Scientists look for factors such as genes, environment, and behavioral traits (including diet) that may contribute to an organism’s lifespan. Altering a factor to see if it changes lifespan can provide evidence about whether or not that specific factor is important for aging. For instance, when researchers suspect that a specific gene has an effect on lifespan, they may test their hypothesis by modifying the activity of that gene (perhaps lower its activity by deleting the gene or increase its activity by adding an extra copy of it). If the life of the animal with the modified gene activity is longer or shorter, then the gene probably does play a role in lifespan.

FACTORS CONTRIBUTING TO LIFESPAN



GENES



ENVIRONMENT



BEHAVIORAL TRAITS

Researchers are finding that lifespan may be influenced by external factors, as well. This has been demonstrated in animal studies. NIA’s Interventions Testing Program (ITP) examines a variety of compounds for their effects on the lifespan of mice. Compounds studied include dietary supplements, hormones, and anti-inflammatory drugs. In one ITP study, male mice treated with aspirin, an anti-inflammatory drug, displayed a moderately increased lifespan. In another ITP study, masoprocol, an anti-inflammatory drug that has antioxidant properties, was found to increase longevity of male, but not female, mice. These and other findings may help scientists identify compounds to test in

UNCOVERING FAMILY SECRETS TO A LONG LIFE

Most of what we know about factors that can contribute to a long lifespan and health span is based on research in animal models. However, NIA-funded research like the Long Life Family Study is taking what we've learned in animals and seeing if it applies to human aging. This study is collecting data from families with at least two siblings who have lived to a very old age in relatively good health. Along with asking questions about their family and health history, the researchers conduct physical assessments and health screenings and collect a small blood sample for genetic tests. What researchers learn about common characteristics shared by these families could one day be used to guide lifestyle advice and medical treatments.

humans for their effects on aging. While some of the compounds tested in the ITP already have a clinical use for humans, scientists are clear: These compounds should be used only as prescribed and not for lifespan extension at this time.

The ability to withstand disease could also be central to lifespan. Studies of exceptionally long-lived people are helping to establish patterns of health decline and increased disease (called morbidity) with old age. For example, do health problems start around the same age in all people and expand over extra years of life for the long-lived, or are the problems delayed, occurring closer to the end of life among exceptional agers? Evidence from a Danish longitudinal study of 92- to 100-year-olds found that health problems seem to be delayed, appearing closer to the end of life. This is not a certain outcome, but in many studies, the average centenarian seems to be in better health than the average 80-year-old. However, living to 100 does not mean never having any health issues. In the New England Centenarian Study, researchers have developed three categories for their long-lived participants. They are characterized as “survivors,” “delayers,” or “escapers,” depending on whether they have survived a life-threatening disease, delayed a serious health problem until much later in life, and/or escaped any serious health events.

Scientists used to think that long life was a good indicator of health span, or years of good health and function. However, some experiments, particularly in mice, demonstrate significant improvements in health, without actually increasing lifespan. For example, NIA scientists and grantees (that is, scientists at a university or other institution whose research is funded by NIA) examining the effects of the wine-derived compound resveratrol in mice on a normal diet found the

compound positively influenced the health of the mice—resveratrol-treated mice had better bone health, heart function, strength, vision, coordination, and cholesterol than the control group. But, resveratrol did not increase lifespan. (Lifespan was increased, however, in mice on a high-fat diet supplemented with resveratrol.)

Understanding how to extend health span—apart from its impact on longevity—is a growing focus of many studies, and for good reason. Imagine a society where a majority of people live to be 100, but along with the added years comes considerably more physical decline. While there is still a place for lifespan research, health span research holds promise for revealing ways to delay or prevent disease and disability so that we can live healthier longer.

Is what's good for mice good for men?

A lot of research findings seem to tell us what is good—or bad—for yeast, mice, roundworms (*C. elegans*), or fruit flies (*Drosophila melanogaster*). Does that mean it will work for you? Animal models are essential to research in the biology of aging. Fruit flies and roundworms, along with more complex organisms like mice, rats, and nonhuman primates, have many biological mechanisms and genes that are similar to humans. They also experience many of the same physiological changes (changes in the body) with aging. Therefore, these animals can be used as models of human aging and human physiology, despite the obvious differences in appearance. Scientists can use some exploratory approaches (like modifying a gene to measure its effects on health or longevity) in animal models such as worms, flies, and mice that would not be possible in humans. They also can better isolate the variable

ANIMAL MODELS

Here are some animals commonly studied in aging research.



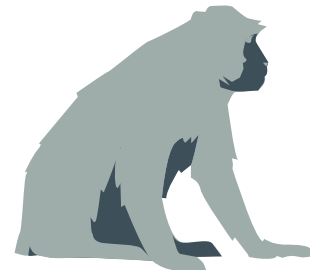
ROUNDWORM
C. elegans



FRUIT FLY
Drosophila melanogaster



MOUSE
Mus musculus



RHESUS MONKEY
Macaca mulatta

they want to investigate because animal studies are conducted in tightly controlled environments. The animals typically have a very structured daily regimen with limited exposure to pollutants, stressors, or other elements that could otherwise affect lifespan and health span.

Different types of studies use different animal models. Animal models with a short lifespan take less time and fewer resources to study from birth to death and to test interventions that might affect the aging process. Scientists might favor a fruit fly when studying a possible genetic target for an intervention to increase longevity, for example, because their average lifespan is only 30 days. This allows researchers to measure the effects in about a month. The roundworm's 2- to 3-week lifespan makes it another ideal model for identifying and studying genes that might affect longevity. In a landmark study, NIA-funded researchers found that reducing the activity of a set of genes, called *daf*, increased roundworm lifespan by three- or even fourfold. *Daf* genes are involved in the roundworm's ability to enter a type of hibernation stage, called diapause, to survive periods of food scarcity. This research would not have been as feasible if conducted using an animal model with an average lifespan of 10 or 20 years.

After scientists establish a possible intervention in one animal model, they then apply the intervention to increasingly complex organisms. They might work their way up from worms or flies to mice and then to larger mammals, such as nonhuman primates. At each step, researchers carefully study if the intervention has the same effect on the comparable

biological pathway. Sometimes it does not. Part of the reason might be that while mice, for example, have only a slightly larger number of genes than worms, and the genes in mice and worms serve similar functions, the activity of mouse genes is different and somewhat more complex than that of worms. As a result, a genetic intervention that increases a worm's lifespan by fourfold might have a significantly less impressive effect on a mouse's lifespan. For similar reasons, an intervention might be promising in mice, but that does not mean it will work the same way or at all in humans.

Studies in animal models closer to humans, such as monkeys or other nonhuman primates, can be key to understanding how basic discoveries might apply to humans. They are essential for pre-clinical studies, an intermediary step between research in animal models like mice and clinical studies in humans. Studies in nonhuman primates, for example, have demonstrated to NIA researchers how normal age-related changes in the heart influence risk of heart disease. They have also been important for testing interventions to lower risks of heart disease, such as drugs to decrease blood vessel stiffness.

So, if something works to slow aging in mice, worms, fruit flies, or monkeys, does that mean it will definitely work for you? The answer is no. Certainly, data from animal studies provide critical insights to the aging process and can form the basis for testing potential interventions. But direct testing in humans is essential before an intervention can be considered safe and effective. ■

A DIFFERENT APPROACH: COMPARATIVE BIOLOGY



MOUSE

Lifespan: 4 years

One approach to aging biology research is called “comparative biology.” It involves comparing two or more similar species that have very different lifespans—one lives much longer than the other—to understand how the longer-lived species has, as one NIA-funded researcher puts it, “exceptional resistance to basic aging processes.” Comparative biology studies generally focus on species that live at least twice as long as their close relatives.

A few possible theories explain what may be taking place among these longer-lived animals:

- ▶ They experience a slower rate of age-related decline.
- ▶ They can survive even when their organs and/or systems break down and have minimal function.
- ▶ They are better able to tolerate cellular damage or diseases.



NAKED MOLE RAT

Lifespan: 17 to 28 years

The naked mole rat, a mouse-size rodent that lives underground, has been widely used in comparative research. It lives approximately 17 years in the wild and more than 28 years in captivity. Its relative, the mouse, lives a maximum of 4 years. What accounts for this startling difference? Naked mole rats have lower metabolic rates and body temperature, meaning that they require less energy to survive. They have low concentrations of blood glucose (blood sugar), insulin, and thyroid hormone, so they are less susceptible to certain diseases. Naked mole rats are better able to withstand some types of biological stress and, at this point, there has never been a case of cancer reported in these animals. All these factors and likely others yet to be determined contribute to their healthier and longer life.





GENETICS

Is aging in our genes?

You may get your hair color from your father’s side of the family and your great math skills from your mother. These traits are “in the genes,” so to speak. Likewise, longevity tends to “run in families”—your genetic make-up plays an important role in how you age. You can see evidence of this genetic connection in families with siblings who live into their 90s or families that have generation after generation of centenarians. These long-lived families are the basis for many genetic studies.

Identifying the genes associated with any trait is difficult. First, just locating the gene requires a detailed understanding of the trait, including knowledge of most, if not all, of the contributing factors and pathways related to that trait. Second, scientists must have clear ways of determining whether the gene suspected to have a relationship with the trait has a direct, indirect, or even no effect on that trait.

Identifying longevity genes is even more complex than determining genes for height or hair color, for example. Scientists do not know all the factors and pathways that contribute to longevity, and measuring a gene's effect on long-lived animals, including humans, would literally take a lifetime! Instead, scientists have identified hundreds of genes that affect longevity in short-lived animal models, like worms and flies. Not all of these genes promote long life. Sometimes mutating or eliminating a gene increases lifespan, suggesting that the normal function of the gene limits longevity. Findings in animal models point to places for scientists to look for the genes that may influence longevity in humans.

How can we find aging genes in humans?

The human genetic blueprint, or genome, consists of approximately 25,000 genes made up of approximately 3 billion letters (base pairs) of DNA. Small deviations in the base pairs naturally occur about once in every 1,000 letters of DNA code, generating small genetic variants. Scientists are finding that some of these variants (polymorphisms) are actually associated with particular traits or chance of developing a specific disease. People with a certain trait, for example, those living past age 100, may be more likely to have one variant of a gene, while people without the same trait may be more likely to have another variant. While it is very difficult to prove that

a gene influences aging in humans, a relationship, or “association,” may be inferred based upon whether a genetic variant is found more frequently among successful agers, such as centenarians, compared with groups of people who have an average or short lifespan and health span.

Several approaches are used to identify possible genes associated with longevity in humans. In the candidate gene approach, scientists look for genes in humans that serve similar functions in the body as genes already associated with aging in animal models, so-called “homologs” or “orthologs” to animal genes. For instance, after finding longevity genes involved in the insulin/IGF-1 pathway of animal models, researchers look for the comparable genes in the insulin/IGF-1 pathway of humans. Scientists then determine whether the genes are linked to longevity in humans by looking to see if a variant of the genes is prevalent among people who live healthy, long lives but not for people who have an average health span and lifespan.

In one NIA-funded project, researchers studied 30 genes associated with the insulin/IGF-1 pathway in humans to see if any variants of those genes were more common in women over 92 years old compared to women who were less than 80 years old. Variants of certain genes—like the *FOXO3a* gene—predominated among long-lived individuals, suggesting a possible role with longer lifespan. This finding provides evidence that, like in animal models, the insulin/IGF-1 pathway has

HUMAN GENETIC BLUEPRINT

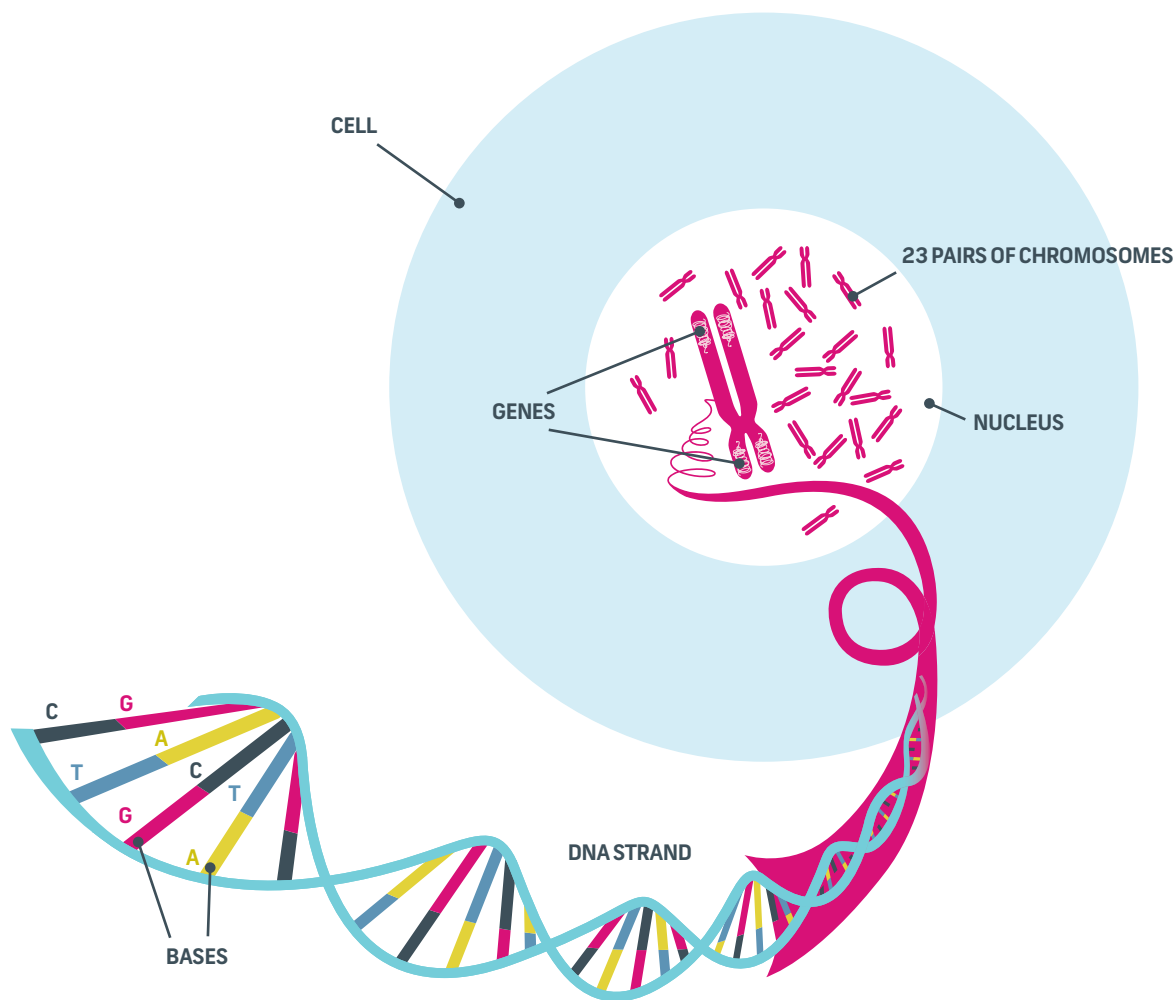


ILLUSTRATION ADAPTED FROM ALZHEIMER'S DISEASE: UNRAVELING THE MYSTERY

The human genetic blueprint, or genome, consists of approximately 25,000 genes made up of approximately 3 billion letters (base pairs) of DNA. Base pair sequences: guanine (G) pairs with cytosine (C); adenine (A) pairs with thymine (T).

Thank You for previewing this eBook

You can read the full version of this eBook in different formats:

- HTML (Free /Available to everyone)
- PDF / TXT (Available to V.I.P. members. Free Standard members can access up to 5 PDF/TXT eBooks per month each month)
- Epub & Mobipocket (Exclusive to V.I.P. members)

To download this full book, simply select the format you desire below

